Update in Primary Care 2010
Landmark Clinical Trials of 2009

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- May 2010

Format
- Confined to Clinical Trials from 2009
- Sources: NEJM, Annals of Internal Medicine, JAMA, ACP Journal Club
- Many, many important trials not included

Gender Health

Prostate CA Screening Background
- #1 Non skin CA in men; 1 in 6 men develop prostate CA over lifetime
- #2 Cause of CA death in men, >27k deaths annually
- Clinically heterogeneous—many never have symptoms
- 2008 USPSTF:
  - Benefit of screening unclear < 75
  - Strong ev no benefit > 75...Recommend against screen > 75

• Prostate CA Screening
  - Ann Intern Med August 5, 2008 vol. 149 no. 3 185-191
  - PLCO Trial 3/2009
  - 76,693 men randomized
  - Annual PSA testing for 6 years
  - Median f/u is 11.5 years

NEJM 360:1310-1319. March 26, 2009
NEJM 360:1320-1328. March 26, 2009
PLCO Trial 3/2009
ERSPC Trial 3/26/09
• 182,000 European men screened
• Median F/U 9 years

• 20% RRR for Prostate CA Death (adjusted P=0.04)
• Absolute reduction 7 CA deaths/10,000 men screened (NNS = 1410)
• 17,000 had biopsies in screened group
• Mortality benefit not until > 10 years

NEJM 360:1320-1328. March 26, 2009

Prostate CA Study Conclusions
• PLCO study showed sig increase in CA detection but no reduction in death with screening program at 10 years.
• ERSPC trial showed divergence of survival curve at year 10—no benefit before. NNS = 1,410. First quality epidemiological evidence
• Reasonable to screen men with life expect > 10 years

Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers
The Selenium and Vitamin E Cancer Prevention Trial (SELECT)


Prostate CA Prevention
• SELECT: Selenium & Vitamin E Cancer Prevention Trial
• Hypothesis: Vit E +/- Selenium will sig reduce incidence of prostate CA over long term.
• Design: 35K men randomized to placebo or variety of preventive strategy. Follow-up q 6 months for 12 years.
• AA >50, others >55, PSA <4, neg DRE, no CA hx, no coagulop
• Vit E 400 IU, Selenium 200µg or both or neither.
• Followed for occurrence of prostate CA, other CA, and death

SELECT Prostate CA Prevention Summary

- Well designed prospective trial of over 35K men
- Intended duration 12 years—stopped after 7 by safety board
- No evident benefit of Vit E or Selenium or Combo
- Duration of trial may be insufficient to detect benefit—average 5.5 year.
- As of 2010 best evidence shows no benefit

USPSTF Breast Cancer Screening: Background

- Most common non-cutaneous CA in woman
- #2 cause of CA death in women—> 40,000 in ‘09
- 2002 USPSTF Rec: Mamo +/- CBE q 1-2 years if 40-69
- In 2005: 68% women 40-65 screened w/i 2 years
- Few receive chemoprevention
- New data prompted new recommendations
- Most controversial recommendations of 2009
**USPSTF Breast CA Summary**

- Little indication to screen more frequently than q 2y
- Screening should be individualized <50 & >75
- No clear preferred radiologic technique
- No clinical benefit to teaching SBE
- Seriously consider prophylactic treatment for women at high risk of breast CA with either tamoxifen or raloxifene

**Primary Care & Pap Smears: Background**

- 11,000 new cases & 4,000 deaths from cervical CA 2008
- Screening frequently continues even in very low risk
- Randomly ID’d from AMA files 2576 MDs
- Survey of practices of 1212 responders:
  - 471 FM
  - 390 IM
  - 333 Ob/Gyn
- Guidelines of ACS, ACOG, USPSTF reviewed in developing questionnaire
1° Care & Pap Guidelines: Conclusions

- Most of us do not adhere to Pap smear guidelines well
- All societies agree: if cervix removed for benign disease, no indication to evaluate cytology of absent organ
- All societies agree: after 65/70 no further paps if previously evaluated and negative
- Good clinical practice— if terminal disease present, no indication for pap
- All agree starting age is 21 or after 1st intercourse

RFA & Barrett’s Esophagus: Background

- Esophageal CA > 500% compared to 1970
- 5 year survival = 15%
- Barrett’s = intestinal metaplasia of lower esophagus → risk adenocarcinoma
- 10% of chronic reflux pts will develop Barrett’s
- High grade dysplasia → 10%/year adenocarcinoma
- Optimal care of dysplasia unknown. Std of care with metaplasia = frequent surveillance. High grade dysplasia → esophagectomy
**Barrett’s & RFA: Design**

- Hypothesis: can decrease dysplasia progression to carcinoma with endoscopically directed RFA
- RFA vs. sham: close surveillance
- 19 centers: 755 screened 127 pts randomized based on severity of dysplasia: 64 low grade, 63 high.
- 2:1 randomization for RFA vs. Sham. 84 ablation: 43 sham
- Endpoints: elimination of metaplasia, progression to higher grade of dysplasia, progression to CA

**Barrett’s & RFA Conclusions**

- RFA produced dramatic elimination of dysplasia & metaplasia
- Only 5 pts progressed to CA: 1 RFA vs. 4 sham
- Study funded by manufacturer of RFA device: BARRX
- Durability of metaplasia/dysplasia reversal unknown: 1-year study
- Extremely promising rx for Barrett’s with dysplasia—applicability to metaplasia unclear—potential huge—long-term trials required

**PPIs & Asthma: Background**

- GER & RAD frequently co-exist
- Reflux may cause bronchoconstriction via microaspiration, acid irritation of upper esophagus or airways.
- ½ of pts with asthma & reflux are asymptomatic regarding reflux & only 5% reflux episodes symptomatic
- Current guidelines recommend evaluating difficult-to-control asthma for GER
- In symptomatic GER—PPI may sig improve RAD

**PPI & RAD: Study Design**

- Hypothesis: Esomeprazole will improve difficult-to-control RAD & pH probe can be used to ID those most likely to benefit.
- Randomized, placebo controlled, 2x blind: pts with poorly asthma on mod/high inhaled steroids. (Poor control = score ≥ 1.5 Juniper Asthma Control Questionaire—scale 0—6—lower better. Or > 1 acute exacerbation requiring unsched med care in last yr.
- 19 centers 2004-2008. Run through Hopkins
- Daily asthma diaries & pH testing during run-in

PPI & RAD: Conclusions

- PPI not effective in improving asthma in patients without symptomatic GER
- pH probe not useful in identifying those who would benefit from PPI
- May not apply to those with symptomatic GER

CV Risk of Clopidogrel + PPI: Background

- Clopid + ASA = standard of care after ACS +/- PCI
- PPI often added for GIB prophylax
- Mechanistic studies show omeperazole inhibits CYP2C19—clopid metabolizing enzyme
- FDA 11/17/09: "The USFDA is recommending that the co-administration of clopidogrel, a drug to prevent blood clot formation, and omeperazole, a PPI used to reduce stomach acid be avoided b/c omeperazole reduces the effectiveness of clopidogrel...at this time the FDA does not have enough information about drug interactions between clopidogrel and other PPIs"

Clopid + PPI: Background

- Retrospective study of all ACS/AMI in VA Hospital data base 2003-2006. 8790 dxed with ACS—8205 filled prescrip.
- 1st end point: all cause mortality or re hosp for ACS, revasc, all cause mort.
- 5244 with PPI, 2961 without (8205 on clopidogrel)
- Median f/u = 521 days
- 59.7% omeperazole, 36.7% multiple PPIs
Clopid + PPI: Conclusions

- Retrospective uncontrolled trial of > 8,000 patients showed PPI associated with 62% increase risk of death or ACS hospitalization
- FDA explicitly recommends not combining omeprazole & clopidogrel
- Deck stacked against PPI in this analysis: PPI group much higher risk for events:
  - 45.5% vs. 38% diabetics
  - 26.4% vs. 20.1% prior MI
  - 25.6% vs. 16.1% PVD
- You decide—is study valid?
- FDA recs against this combo: consider H2 blockers or other PPI (except cimetidine & esomeprazole)

### Table 2: Adverse Outcomes Following Hospital Discharge for Acute Coronary Syndrome (ACS)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel (n = 290)</th>
<th>Aspirin (n = 252)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or readmission to ACS</td>
<td>0.05 (20)</td>
<td>0.17 (32)</td>
<td>1.00 (0.45-1.80)</td>
<td>1.05 (0.45-1.80)</td>
</tr>
<tr>
<td>Retrospective stroke</td>
<td>0.00 (0)</td>
<td>0.00 (0)</td>
<td>1.50 (0.39-6.6)</td>
<td>1.50 (0.39-6.6)</td>
</tr>
<tr>
<td>Rehospitalization to ACS</td>
<td>0.00 (0)</td>
<td>0.00 (0)</td>
<td>1.25 (0.52-3.0)</td>
<td>1.25 (0.52-3.0)</td>
</tr>
</tbody>
</table>

- Ho, PM, et al. JAMA 2009;301(9):937-44 March 4, 2009

### Clopidogrel + ASA in AF: Background

- 1% of Americans have AF; 10% if > 80 yo
- AF increases stroke risk on average 5x.
- Vit K antagonists < risk 66%; ASA < risk 22% on ave.
- Many poor warfarin risk: risk of ICH, frequent lab tests, many drug/food interactions
- ACTIVE W: warfarin vs. ASA + Clopid: terminated early b/c warfarin superiority
- ACTIVE A: ASA vs. ASA + Clopid
- 580 centers; 33 countries
- Eligible if CAF or PAF in last 6 months
- Clopid 75 + ASA 75/100 vs. ASA 75/100 alone

### Table 3: Relative Risk of Primary and Secondary Outcomes, According to Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel plus Aspirin (n = 292)</th>
<th>Aspirin (n = 254)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>832 (832)</td>
<td>794 (794)</td>
<td>0.89 (0.81-0.98)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death</td>
<td>256 (256)</td>
<td>219 (219)</td>
<td>0.72 (0.62-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>398 (398)</td>
<td>334 (334)</td>
<td>0.40 (0.32-0.49)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>39 (39)</td>
<td>28 (28)</td>
<td>1.39 (0.89-2.19)</td>
<td>0.18</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>1.00 (0.10-10)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

- Ho, PM, et al. JAMA 2009;301(9):937-44 March 4, 2009

### Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

#### ABSTRACT

**ORIGINAL ARTICLE**

**Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation**

The ACTIVE Investigators

**NEJM 2009;360:2066-78. May 14, 2009**
ACTIVE A: Conclusions

- RRR for disabling stroke 24% per year in combo
- ARR for disabling stroke 0.5% per year
- NNT per year = 200
- RRH: major hemorrhage 54% per year
- ARH: major hemorrhage 0.7%
- NNH per year = 143—NNK = 1000
- Subgroup analysis showed no benefit if:
  - Age < 65 or > 75
  - CHADS $\leq$ 1
  - PAF
- Warfarin remains DOC for CHADS >2—little support for addition of clopidogrel

Warfarin & Pharmacogenomics: Bkg

- 30 mil prescrip in US in 2004
- Dosing range 10x between pts.
- Clinical factors greatly affect dose requirements: mass, diet, concomitant meds
- Genetic factors affect dose requirements:
  - CP450—CYP2C9
  - Vit K epoxide reductase complex—VKORc
- 2007 FDA added pharmacogenomic data to product label—no indic how to use
- Look @ 6,000 pts. in pharmacogen consortium
Warfarin Pharmagenomics: Conclusions

- Dose extremes difficult to predict
- Pharmagenomics don’t help in middle dose ranges
- Can help sig predict who will require dose extremes
- 40% of patients dosed at extremes
- Genetic variants common:
  - CYP variants 25%
  - VOKR variants 68%
- More data to come
- Will not need to know gene mutations: very likely will have lab generated algorithms to predict starting dose.

Clopidogrel Pharmacogen: Bkg

- French Acute ST & Non-ST Elev MI Investigators—FAST-MI
- 785,000 new ACS in USA this year—470,000 recurrent events
- 5-45% of pts on platelet inhibitors will have 2nd event—failure
- Dual antiplt rx freq prescribed post MI—always post PCI
- Interindividual variability in response to clopid may dictate success/failure of dual regimen
- Clopid is a prodrug which must be metabd by CP450 b-4 inhibiting ADP mediated plt aggregation
- Genes encoding CP450 are polymorphic
- Response may also be affected by intest absorp
Clopid Pharmacogenomics: Bkg

- Relation between gene polymorphisms (SNPs) regulating absorb & metabolism & clinical events explored in this study. Hypothesis: can predict cardiac events based upon genes regulating clopid.
- Looked at complete data base of all pts admitted to ICUs in France with MI—over 2 months, 223 hospitals
- Followed pts for 1 year who received clopid. All rxd same—just blood banked & DNA analyzed
  - 99.2% f/u
  - Typed for 4 genes; looking at major known variants
  - 3670 enrolled, 2208 contributed DNA & were on clopid


Clopid Pharmacogen: Conclusions

- Tests for mutations in the genes coding for absorption & metabolism of clopidogrel can predict antiplt effect invitro.
- Such genetic tests can predict risk of future cardiac events in very high risk populations.
- If have 2 variant alleles at the CYP2C19 locus then have 3.58 x risk of event in 1 year compared to wild type if have PCI. 1.98x risk if ACS without PCI.
- 28.7% have 1 variant. Only 3% in this study had 2 variant alleles—1 allele posed no increased risk. Other smaller trials show increased risk with 1 allele.
- 31-37% have polymorphisms at absorption gene increasing risk 1.5x

Ray WA. Et al. NEJM 2009;360:225-35 Jan 12, 2009
Antipsychotics & CV Death: Bkg

- Risperidol, Zyprexa, Seroquel among top 10 selling drugs in 2007
- Dose related > sudden death with old antipsychotics
- Block K⁺ repolarizing currents, prolong QT
- Hypothesis: New generation anti-Ψ won’t increase CV death
- Retro review of all TN Medicaid patients 2000-2005 filling at least 2 anti-Ψ prescrip & ≥2 outpatient visit in prev 2 years. 2 controls for each user.
- Evald: thioridazine, haloperidol, clozapine, quetiapine, olanzapine, risperadone
- Sudden CV death 1st endpoint
- 13,300 users, 186,600 controls. 1,042,159 person years f/u


Antipsychotics & CV SD: Conclusions

- Antipsychotics associated with about a 0.2% risk of SD per year of use.
- NNK with typical agents = 870
- NNK with atypical = 1389
- NNK with high dose = 298
- These agents should be used with sig caution in those at high risk for CV event. Seriously consider EKG B-4 & during high dose use—not CV safer than older agents


Ginko & Memory: Background

- 2008 GEM investigators: Ginko does not prevent Alzheimers
- Ginko biloba world’s most commonly used agent to promote memory health.
- Hypothesis: daily supplementation of G. biloba 120 bid will prevent cognitive decline in those at risk.
- 3702 older (mean = 79.2), non-demented adults randomized to G. biloba 120 bid or placebo
- Median f/u = 6.1 years
- Followed a variety of cognitive function parameters

Ginko & Cog Decline: Conclusions
- Largest study to date on use of this agent
- Standardized dosing—so ideal dose unknown
- Large dropout—40% not taking drug by study end
- No change in cognitive performance at any stage or in any parameter
- Subgroup analysis: No benefit regardless of age, presence/absence of MCI, APOE4
- Only included whites
- No benefit to G biloba at this time.

2009 Landmark Trial Summary
- PSA Screening for life expectancy > 10 years indicated
- Selenium & Vit E for prostate CA prevention: No ben
- Breast CA Screening: Individualize b-4 50 and after 75. Stop SBE. Consider preventive rx.
- Pap Smears: Start @21, stop for no cervix, stop @65-70
- Barrett’s: RFA on horizon—look for it
- Asthma: PPIs don’t help if no GERD symptoms
- PPI & Clopid: FDA says no omeperazole. Clin data weak. Use H-2 antagonist or other PPI for now

2009 Landmark Trial Summary
- Clopid + ASA for AF: NNT = 200; NNH = 143
- Pharmacogenomics for Warfarin dosing: On horizon to plan dosing schedule
- Pharmacogenomics for Clopidogrel: On horizon to dictate dose or alternative
- Atyp Antipsychotics: increase sudden death. NNK = 298 with high dose
- Ginko: does not improve elderly cognitive performance nor hinder decline